REMARKS

This paper is filed in Response to the Office Action mailed January 3, 2007. Claims 1, 2, 4 and 7 to 16 are pending and under consideration. New claims 54 to 65 have been added. Accordingly, upon entry of this response, claims 1, 2, 4, 7 to 16 and 54 to 65 are under consideration.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the specification. In particular, the amendments to claims 1 and 14 to 16 to recite that the "functional fragment" specifically binds to, inhibits cell proliferation or induces apoptosis of at least one of the recited cell lines was made in order to more clearly indicate that the functional fragment has binding activity, inhibits cell proliferation, or induces apoptosis. The amendments to claims 1, 7, 8 and 15 to recite the various percent identities are supported, for example, at page 13, lines 23, to page 14, line 3; and page . The amendment to claim 2, to recite that the antibody or functional fragment inhibits cell proliferation of CACO-2....or COLO-206F....cells" is supported, for example, at page 3, lines 6-18, page 47, lines 16-24, and page 48, line 26, to page 49, line 5. The amendment to claim 4, to recite that the antibody or functional fragment induces apoptosis of at least one of HT-29,....CACO-2,....COLO-320,....COLO-206F....or COLO-678....cells" is supported, for example, at page 2, lines 13-25, page 47, lines 16-24, and page 48, line 26, to page 49, line 5. The remaining amendments to claims 9 to 13 were made in view of the foregoing amendments or to provide greater antecedent basis. Thus, as the claim amendments are supported by the specification or were made to address informalities, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 54 to 65 are supported throughout the specification. In particular, the recitation of the various percent identities in claims 54 to 62 are supported, for example, as set forth above at page 13, lines 23, to page 14, line 3. The recitation of "identical to 100 contiguous amino acids" in claims 57 to 62 is supported, for example, at page 10, lines 4-15. New claim 63, directed to an antibody that comprises SEQ ID NO:1 and SEQ ID NO:3 with a conservative substitution in either SEQ ID NO:1 or SEQ ID NO:3 is supported, for example, at page 14, lines 14-17; and page 23, line 24, to page 24, line 9. New claims 64 and 65 are supported, for

example, at Figures 1 and 2. Thus, as the new claims are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Specification

The disclosure stands objected to due to an embedded hyperlink. Applicants have amended the specification to delete the hyperlink. In view of the amendment, Applicants respectfully request that the objection to the specification be withdrawn.

Regarding the Claim Objections

Claims 2 and 4 stand objected to due to being in improper dependent form. Claims 2 and 4 have been amended so as to be in proper dependent form. In particular, dependent claim 4 has been amended to be narrower in scope than claim 2. In view of the amendments, Applicants respectfully request that the objection to claims 2 and 4 be withdrawn.

I. REJECTIONS UNDER 35 U.S.C. §112

The rejection of claims 1, 2, 4, 7 to 11, 14 and 15 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. Allegedly the specification does not enable the skilled artisan to make and use the invention commensurate in scope with the claims.

Claims 1, 2, 4, 7 to 11, 14 and 15 as originally filed are adequately enabled. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed with respect to the amended and new claims.

It appears that there are five grounds for rejection, allegedly 1) the claimed functional fragments need not bind to an antigen; 2) the claims do not enable structures other than antibodies; 3) the claims are directed to polypeptides that only have one heavy or light chain variable region; 4) the claims are not enabled for antibodies that bind to any cancer cell, only the recited cell lines; and 5) claim 14 includes fragments that may not bind or be capable of inducing apoptosis.

In terms of the first ground for rejection, the amended and new claims recite that the functional fragment binds to particular cell types. Furthermore, the skilled artisan understands that a functional fragment of an antibody that binds to a cell has the appropriate repertoire of heavy and light chain variable sequences to mediate binding to cell antigen. Thus, the claimed

functional fragments bind to particular cell types and therefore have the appropriate repertoire of heavy and light chain variable region sequences to mediate binding to cell antigen.

In terms of the second ground for rejection, the amended and new claims recite antibodies and functional fragments and therefore, the structures are antibody structures. Thus, as the amended claims are directed to antibodies and functional fragments, this ground for rejection is moot.

In terms of the third ground for rejection, the amended and new claims recite antibodies and functional fragments which, as discussed above contain heavy chain and light chain variable regions. Thus, as the amended claims are directed to antibodies and functional fragments that have heavy and light chain variable region sequences, this ground for rejection is moot.

In terms of the fourth ground for rejection, the amended and new claims are directed to antibodies that bind to one or more particular cell lines. Thus, as the claimed antibodies and functional fragments bind to one or more particular cell lines, this ground for rejection is moot.

In terms of the rejection of claim 14, and whether fragments V_L, V_H, F_C, have the ability to bind to or induce apoptosis of cells, claim 14 has been amended to delete reference to V_L, V_H, F_C. Applicants also respectfully directed the Examiner's attention to Exhibit A, submitted herewith. Exhibit A is cell proliferation data generated with an F_v fragment comprising SEQ ID NOs:1 and 3.

In brief, antibody was subjected to a buffer exchange with 100 mM sodium citrate (pH 3.5) using NAP^{tm} – 10 columns (Amersham Pharmacia Biotech) prior to pepsin digestion. For each milligram of antibody, 5 µg pepsin (Sigma Aldrich, Taufkirchen, Germany) was added, followed by incubation for 10-15 min in a 37° C water bath. The reaction was terminated by adding 1/10 volume of 3.0 M Tris (pH 8.8) followed by centrifuging at 10,000 g for 30 min. Pepsin digestion was also done with an unrelated control Human IgM antibody (Chrompure IgM, Dianova, Hamburg, Germany). Prior to apoptosis studies F_v fragment and human control IgM fragment were dialyzed against PBS. SDS gel electrophoresis and Western blotting confirmed pepsin cleavage of both antibodies. The MTT cell proliferation assay disclosed in the specification (page 48, lines 1-25) was used to study the effect on cell proliferation, with the results illustrated in Exhibit A.

The data in Exhibit A demonstrate that such a fragment retains the ability to bind to and inhibit cell proliferation of pancreatic cancer cells. Thus, the data corroborates that functional fragments retain native full length antibody 1) binding; and 2) anti-cell proliferative activity.

In view of the foregoing remarks, claims 1, 2, 4, 7 to 11, 14 and 15 as amended are adequately enabled. Accordingly, Applicants respectfully request that the enablement rejection under 35 U.S.C. §112, first paragraph be withdrawn.

The rejection of claims 1, 2, 4, 7, 8, 12 and 15 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. Allegedly the claimed subject matter is not described in the specification to one skilled in the art that the inventor at the time the application was filed had possession of the claimed invention.

Claims 1, 2, 4, 7, 8, 12 and 15 as originally filed are adequately described. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed with respect to the amended and new claims.

A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). In order to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976). Furthermore, the Federal Circuit recently held "that (1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, a genus of molecules can be adequately described under 35 U.S.C. §112, first paragraph without specific examples, an actual reduction to practice, or a complete structure of antibodies and functional fragments.

Here, in view of the guidance in the specification, which discloses antibody variable heavy and light chain sequences (e.g., SEQ ID NOs:1 and 3), and knowledge in the art regarding

antibody structure and function and functional fragments, the skilled artisan would be apprised of other antibodies and functional fragments within the scope of the claims. Consequently, the amended and new claims are adequately described.

In this regard, the specification teaches antibody heavy and light chain variable sequences (e.g., SEQ ID NOs:1 and 3). The specification also teaches functional fragments, such as F_V, Fab, Fab', and $F(ab')_2$, which are well established in the art as retaining at least a partial function of native full length antibody function, such as binding.

The level of knowledge and skill in the art with respect to antibody structure and function was high at the time of the invention. Evidence of such knowledge regarding antibody structure and function, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of framework regions is acknowledged by the Examiner in the Action, at pages 5 and 6. Of particular note, this discussion of antibody structure and function is prefaced by the statement that "it is well established in the art that...." Functional fragments, such as F_V, Fab, Fab', and $F(ab')_2$, are disclosed in the specification and are well established in the art as retaining at least a partial function of native full length antibody function, such as binding. Antibodies and functional fragments can be readily produced using conventional methods disclosed in the specification (for example, page 19, line 21, to page 24, line 9) or known in the art at the time of the invention. Thus, in view of the high degree of knowledge in the art about antibody structure and function at the time of the invention, when combined with the disclosure in the specification of the heavy and light chain variable sequences, SEQ ID NOs:1 and 3, the skilled artisan would be apprised of a number of antibodies and functional fragments within the scope of the claims.

In terms of the Examiner's concern regarding no description of the antigen to which the antibodies bind, as discussed, the claimed antibodies and functional fragments are described 1) structurally- they have a high percentage of identity (at least 85%) to heavy and light chain variable sequences, SEQ ID NOs:1 and 3; and 2) functionally- they bind to at least one of the recited cells types. Thus, as the claimed antibodies and functional fragments are described structurally, having a high degree of sequence identity to SEQ ID NOs:1 and 3, and functionally, the skilled artisan would be apprised of a large number of additional antibodies and functional fragments within the scope of the claims.

Furthermore, the antigen to which the claimed antibodies bind is obviously present on at least one of the cell types recited in the claims. Thus, the antigen can be considered described because of its presence on at least one of these cell types. Moreover, as discussed above the written description requirement may be satisfied without examples or an actual reduction to practice. In view of the fact that 35 U.S.C. §112, first paragraph can be satisfied without examples or an actual reduction to practice, it is clear that the written description requirement can also be satisfied without describing the antigen to which the claimed antibodies and functional fragments bind.

Thus, in view of the specification and knowledge in the art at the time of the invention, the skilled artisan would be apprised of sufficient structural and functional characteristics of antibodies and functional fragments. As such, an adequate written description of the amended and new claims is provided, and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description be withdrawn.

II. REJECTION UNDER 35 U.S.C. §102(e)

The rejection of claims 1, 2, 4 and 13 under 35 U.S.C. §102(e) as allegedly anticipated by Zhou *et al.* (US Patent Application Publication 2003/01900687) is respectfully traversed. Allegedly, Zhou *et al.* describe an antibody that binds to TRAIL thereby anticipating the claims

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990), *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990).

Claims 1, 2, 4, and 13 have been amended to recite that the claimed antibodies and functional fragments comprise "a sequence at least 85% identical to the amino acid sequence of SEQ ID NO:1 and a sequence at least 85% identical to the amino acid sequence of SEQ ID NO:3." Zhou *et al.* fail to teach or suggest an antibody or functional fragment thereof having the high degree of sequence identity to SEQ ID NOs:1 and 3. For example, the N-terminal 20 amino acid sequence of the heavy chain variable sequence of TRA-8 antibody described in Zhou *et al.* does not have any amino acid residues identical to the N-terminal amino acid sequence of the heavy chain variable region of SEQ ID NO:1 (Figure 1), for a percent identity of 0%. The N-terminal 20 amino acid sequence of the light chain variable sequence of TRA-8 antibody described in Zhou *et al.* only has two amino acid residues identical to the light chain variable

region of SEQ ID NO:3 (Figure 2), for a percent identity of 10%. A humanized form of TRA-8 described in Zhou *et al.*, which altered 19 residues of light chain variable region at positions 8, 9, 10, 11, 13, 20, 42, 43, 60, 63, 77, 78, 80, 83, 85, 87, 99, 103 and 108 (see, [0392], SEQ ID NO:46), did not have a single identical amino acid to SEQ ID NO:3 at any of these positions. Three additional humanized forms of TRA-8 described in Zhou *et al.*, which altered 11 (H1), 9 (H3) or 6 (H4) residues of heavy chain variable region at various positions (see, [0515]-[0517], SEQ ID NO:56, 59 and 60), also did not have a single identical amino acid to SEQ ID NO:1 at any of these positions.

In view of the foregoing, Zhou *et al.* (US Patent Application Publication 2003/01900687) fail to teach or suggest the claimed antibodies and functional fragments thereof. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(c) be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1, 2, 4, 7 to 16 and 54 to 65 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP

Date: May 14, 2007

Robert M. Bedgood, Ph.D.
Reg. No. 43,488

Customer No. 25700
12255 El Camino Real, Suite 300
San Diego, CA 92130
Telephone: (858) 509-4065
Facsimile: (858) 509-4010

EXHIBIT A
Antibody Fragment Maintains Anti-Cell Proliferative Effect